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In vivo imaging of radiopaque resorbable inferior vena cava filter infused with gold nanoparticles

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Abstract

Radiopaque resorbable inferior vena cava filter (IVCF) were developed to offer a less expensive alternative to assessing filter integrity in preventing pulmonary embolism for the recommended prophylactic period and then simply vanishes without intervention. In this study, we determined the efficacy of gold nanoparticle (AuNP)-infused poly-p-dioxanone (PPDO) as an IVCF in a swine model.

Infusion into PPDO loaded 1.14±0.08 % AuNP by weight as determined by elemental analysis. The infusion did not alter PPDO's mechanical strength nor crystallinity (Kruskal−Wallis one-way ANOVA, $p<0.05$). There was no cytotoxicity observed (one-way ANOVA, $p<0.05$) when tested against RF24 and MRC5 cells. Gold content in PPDO was maintained at ~2000 ppm during the 6-week incubation in PBS at 37°C.

As a proof-of-concept, two pigs were deployed with IVCF, one with AuNP-PPDO and the other without coating. Results show that the stent ring of AuNP-PPDO was highly visible even in the presence of iodine-based contrast agent and after clot introduction, but not of the uncoated IVCF. Autopsy at two weeks post-implantation showed AuNP-PPDO filter was endothelialized onto the IVC wall, and no sign of filter migration was observed. The induced clot was also still trapped within the AuNP-PPDO IVCF.

As a conclusion, we successfully fabricated AuNP-infused PPDO IVCF that is radiopaque, has robust mechanical strength, biocompatible, and can be imaged effectively in vivo. This suggests the efficacy of this novel, radiopaque, absorbable IVCF for monitoring its position and integrity over time, thus increasing the safety and efficacy of deep vein thrombosis treatment.

Keywords

Gold nanoparticles (AuNP); inferior vena cava filter (IVCF); pulmonary embolism; x-ray and computed tomography (CT); poly-*p*-dioxanone (PPDO)

1. INTRODUCTION

An inferior vena cava filter (IVCF) is deployed in patients who are contradicted with anticoagulant agents to prevent pulmonary embolism [1, 2]. The intended dwell time of a temporary IVCF is 7 to 35 days [3]. These IVCF is to be surgically retrieved once the risk of thromboembolic disease is reduced to prevent filter fracture and perforation due to prolonged use. However, the rate of temporary IVCF retrieval is less than 60%, and the prolonged IVCF dwell time presents a challenge to successful retrieval and life-threatening complications including vessel puncture and IVCF migration. Thus, an absorbable IVCF made from poly-p-dioxanone (PPDO) was developed. PPDO has a favorable degradation profile that can ensure the mechanical strength and integrity of the ICVF with in the intended dwell time, but it will degrade after the intended use and avoid the necessity of another surgical retrieval procedure. Therefore, PPDO-based IVCF could enhance the safety and decrease medical cost while maintaining the efficacy of the IVCF. However, PPDO is radiolucent and cannot be monitored under conventional imaging modalities, such as X-ray and computed tomography (CT). Thus, the purpose of our research is to develop the first totally absorbable, radiopaque IVCF, whose position and integrity can be easily monitored under X-ray and CT. The clinical implication is to avoid fatal complications associated with failure of retrieval of temporary IVCF. Our previous research has successfully demonstrated the feasibility of radiopacity enhancement by infusing iodine and gold nanoparticles (AuNPs) into PPDO [4, 5]. Our current research continues to investigate the enhanced material discrimination of AuNPs compared to iodine on dual energy CT (DECT) and the impact of AuNP infusion on in vivo imaging and behavior of PPDO IVCF.

2. MATERIALS & METHODS

Four nanometer AuNPs were synthesized, characterized and infused into PPDO. The ultraviolet–visible (UV-Vis) profile of AuNPs was monitored on a Cary 60 UV–Vis spectrophotometer (Agilent Technologies, Santa Clara, CA). Particle size was determined on

a JEOL 1230 high contrast transmission electron microscope (TEM; JEOL USA, Inc., Peabody, MA) equipped with a digital camera. Infused gold was quantified via elemental analysis on a Varian 720ES inductively coupled optical emission spectrophotometer (ICP-OES; Agilent Technologies). Radiopacity was evaluated on an X-ray (MX-20 digital cabinet x-ray, Faxitron Bioptics, Tucson, AZ) and micro-CT (a CT-eXplore Locus RS preclinical *in vivo* scanner, GE Medical Systems, London, ON, Canada). Cytotoxicity was tested against RF24 and MRC5 cells. The stability of infusion over a 10-week period was also determined in terms of radiopacity and amount of AuNP retained in the PPDO.

Multiple agar and blood phantoms of varying concentrations of hydrophilic AuNPs and a commercial iodine contrast agent, Visipaque™, were constructed. Preliminary determination of the detection limit of AuNPs in blood and the energy dependence of AuNPs and iodine was performed on a GE DISCOVERY CT750HD dual energy CT (DECT; Discovery CT 750HD; GE Healthcare, Milwaukee, WI). Material discrimination was achieved in MATLAB 8.5 and Statistics Toolbox 8.5 (The MathWorks, Inc., Natick, MA) via creation of a bisector line.

The radiopacity and mechanical strength of AuNP-PPDO IVCF were evaluated in swine model. Autologous thrombi were introduced one week after the deployment. The radiopacity and ability to capture thrombi was evaluated by CT and compared with uncoated PPDO IVCF. Autopsy was performed to evaluate in vivo toxicity and filter endothelialization.

3. RESULTS AND DISCUSSION

Gold nanoparticles that were synthesized had an average diameter of 4 nm as shown in the TEM (Figure 1A). It has a characteristic absorption peak at 520 nm as shown in the UV-vis absorption profile (Figure 1B). AuNP infusion enhanced the radiopacity of PPDO (Figure 2). Quantification by elemental analysis showed the presence of gold in AuNP-infused PPDO sutures (1.14±0.08 % by weight), but not in untreated PPDO sutures (0.19±0.01 % by weight). This gold content in PPDO was maintained at approximately 2000 ppm during the 6-week incubation in PBS at 37°C (Figure 2). The infusion also did not alter PPDO's mechanical strength nor crystallinity (Kruskal−Wallis one-way ANOVA on ranks, $p<0.05$). In terms of in vitro cytotoxicity, no cytotoxicity was observed (one-way ANOVA, $p<0.05$) when evaluated on immortalized human vascular endothelial cell RF24 cells and normal lung fibroblast MRC5. This suggests that no significant difference in cell viability among the treatment groups, or between the treatment groups and the control group (one-way ANOVA, $p<0.05$) (Figure 3) [4].

Material discrimination between gold and iodine on DECT was performed to evaluate the ability to differentiate AuNP-PPDO IVCF in the presence of iodine based contrast agent when the filter is deployed *in vivo*. The prediction of correlation between Hounsfield Unit (HU) value and AuNP and iodine concentrations was studied to evaluate the feasibility of monitoring the integrity of the AuNP-PPDO IVCF from DECT HU readings. AuNP concentration needed to be greater than 0.5 mg/ml at 70 keV for visualization (contrast-to-noise ratio >2). Material discrimination between gold and iodine gave good prediction of

correlation between HU value and AuNP and iodine concentrations except for very low AuNP (0–1 mg/mL) (Figure 4).

The radiopacity of the AuNP-PPDO IVCF was evaluated on micro-CT in comparison with an uncoated control PPDO-IVCF (Figure 5). Results in Figure 5 show that there is an increased signal with AuNP-coated IVCF compared to the uncoated one. This clearly demonstrates the enhanced radiopacity of the nanoparticle-coated IVCF that could help us in monitoring the position and integrity during and after the deployment of the filters.

As a proof-of-concept, two pigs were deployed with IVCFs, one with AuNP-PPDO and the other without coating. Figure 6 shows the CT axial view of the two pigs. The stent ring of the AuNP-PPDO IVF was clearly visible but not the uncoated PPDO IVCF. Figure 7 shows the axial CT image of the pig deployed with the AuNP-PPDO IVCF after the clot introduction and in the presence of iodine based contrast agent. The inset shows the zoomed-in image of the IVCF location. The yellow circle defines the stent of the AuNP-PPDO IVCF. The iodine contrast shows blood flow in the IVC (blue arrow) and the aorta (red arrow). The black arrow shows the clot that was introduced and was confined within the AuNP-PPDO IVCF.

According to a pilot study performed on PPDO ICVF, endothelialization of the stent portion should occur within two weeks after the deployment [3]. Thus, autopsy was performed at two weeks post deployment to evaluate the entothelialization. Figure 8A shows PPDO ICVF at 19 days post deployment from our previously published data [3]. The stent had been endothelialized into the vessel wall, and the introduced clot was still captured in the filter. Figure 8B shows that the stent of the AuNP-PPDO IVCF was also endothelialized onto the IVC wall two weeks post deployment, and no sign of filter migration was observed. The introduced clot was also still trapped within the AuNP-PPDO filter. Thus AuNP infusion did not affect the endothelialization process of the PPDO ICVF or its ability to capture and trap circulation clot.

Figure 9 shows the H&E staining of the IVC containing the uncoated PPDO IVCF (Figure 9A) and AuNP-PPDO IVCF (Figure 9B). The oval spaces in Figure 9A and 9B are the endothelialized PPDO fibers. The structure of the IVC containing AuNP-PPDO IVCF is similar to that containing the uncoated PPDO IVCF, and no toxicity was observed. This result concurs with the *in vitro* cytotoxicity study that AuNP-PPDO IVCF are biocompatible.

4. CONCLUSION

We successfully developed a radiopaque, biocompatible and robust AuNP-infused PPDO IVCF. The efficacy of a novel radiopaque nanoparticle-based resorbable IVCF was evaluated both *in vitro* and *in vivo.* Preliminary pig study clearly showed the visibility of AuNP-PPDO IVCF in conventional clinical CT, even in the presence of clot and iodine contrast agent, which indicates the ability to differentiate AuNP-PPDO IVCF from iodine contrast agent and clot. Endothelialization and function of the IVCF was maintained. This suggests the efficacy of this novel, radiopaque, absorbable IVC filter for monitoring its position and

integrity over time, thus increasing the safety and efficacy of deep vein thrombosis treatment.

ACKNOWLEDGMENTS

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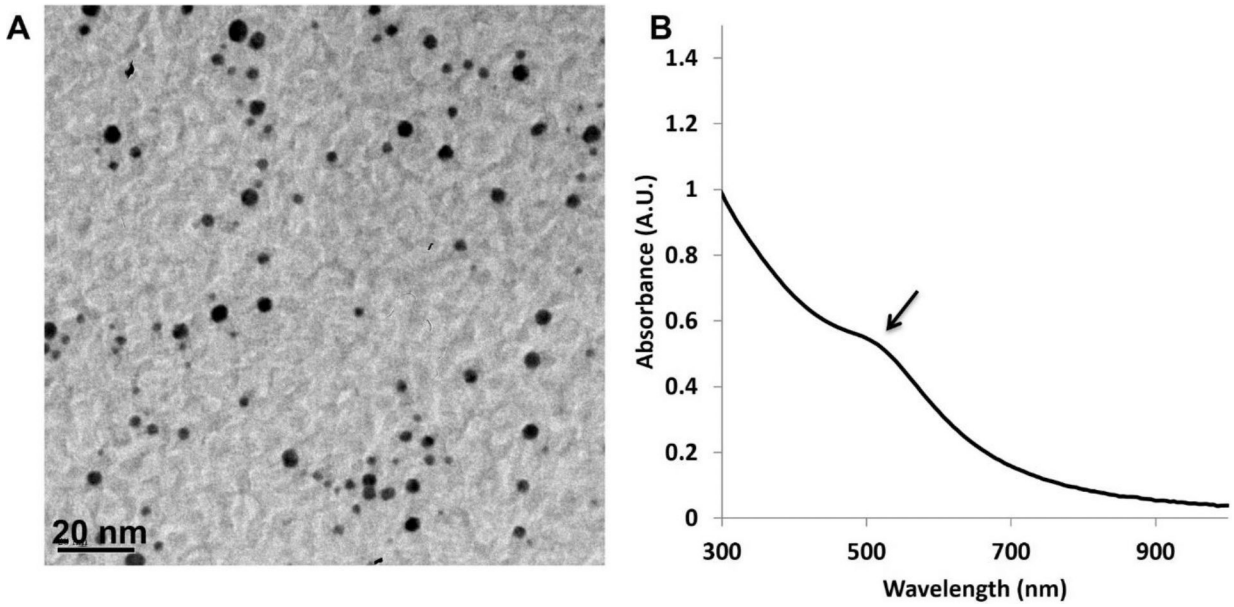


Figure 1.

Hydrophobic 4-nm gold nanoparticles were successfully synthesized. TEM and UV-Vis spectrum of 4-nm AuNPs. The transmission electron microscopy (TEM) result (A) is consistent with the ~520 nm peak (shown by the arrow) on the UV-Vis spectrum (B) for the 4-nm AuNPs [4].

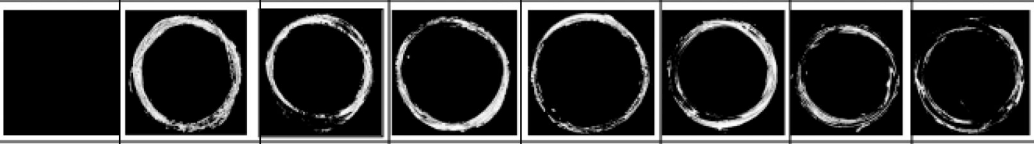
	No Coating	AuNP-coated PPDO						
	Week 0	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Micro-CT imaging								
ppm Au	2.6 ± 1.7	1974 ± 107	1909 ± 112	1950 ± 54	1809 ± 14	2011 ± 15	1972 ± 44	1824 ± 90

Figure 2.

Long-term imaging and gold content of infused PPDO sutures. AuNP-infused PPDO sutures were soaked in PBS at 37°C. Three sutures were sampled each week and dried under vacuum. Radiopacity was imaged by micro-CT. The gold content was measured by ICP-OES, and the quantification in ppm is listed under the representative image of each week. All AuNP-infused PPDO sutures maintained radiopaque under micro-CT and there was no significant decrease of gold content (one way ANOVA, $p = 0.778$) [4].

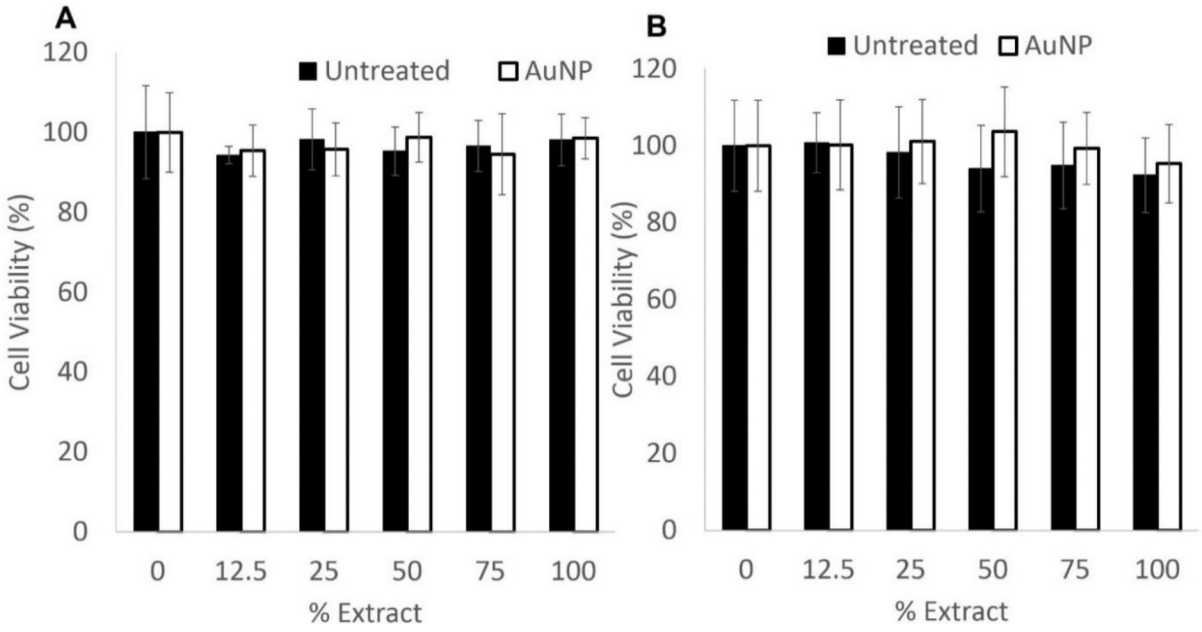


Figure 3.

Infusion with AuNPs did not increase cytotoxicity. Control and AuNP-infused PPDO sutures were subjected to extraction in MEM for RF24 (A) and EMEM for MRC5 (B) and diluted to various concentrations. The cytotoxicity of each concentration on RF24 and MRC5 cells was evaluated. No significant difference in cell viability was found between the treated groups and the control group (one-way ANOVA, $p<0.05$) [4].

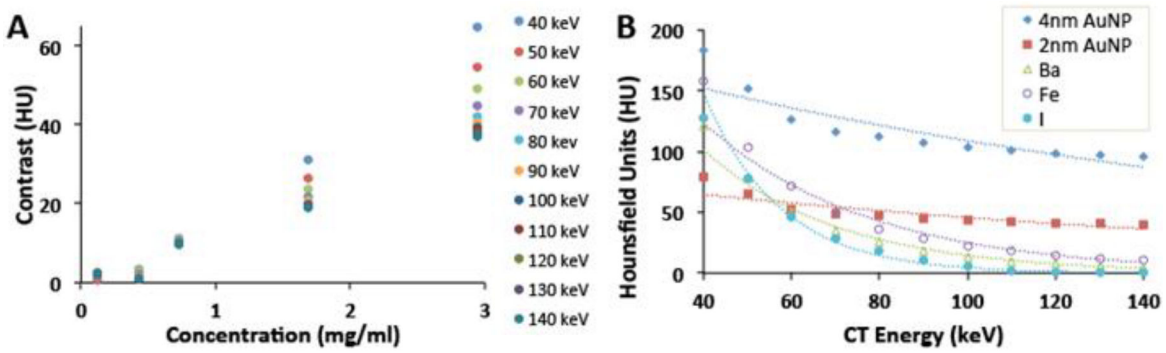


Figure 4.

Material discrimination on DECT. (A) Contrast versus AuNP concentration in blood for mono- energetic reconstructions. (B) HU versus CT energy contrast in water.

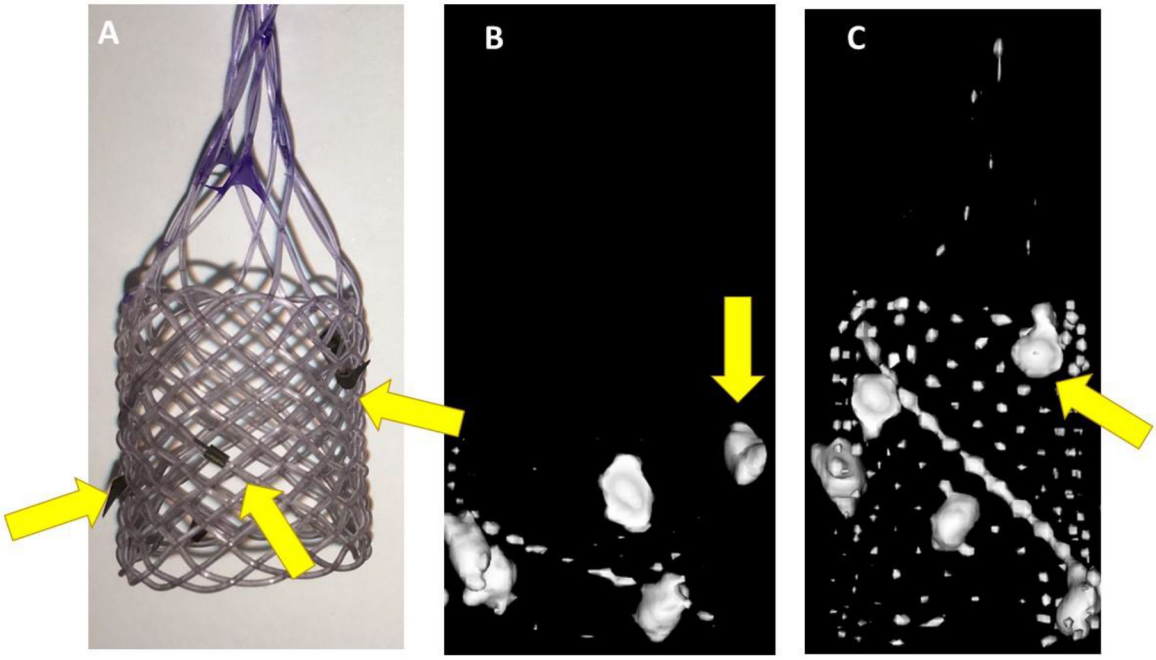


Figure 5.

MicroCT (micro-CT) of AuNP-PPDO IVCF and uncoated PPDO IVCF. (A) PPDO IVCF. The yellow arrows point out the steel barbs that serve as anchors and radiopaque markers; (B) Uncoated PPDO IVCF on micro-CT. The steel barbs (one of which is pointed out by the yellow arrow) are visible but not the filter itself; (C)AuNP-PPDO IVCF on micro-CT. AuNP infusion clearly enhanced the radiopacity of the IVCF, and the contour of the IVCF is clearly shown in the micro-CT image. The yellow arrow point out one of the steel barbs, which gave a bright signal on micro-CT.

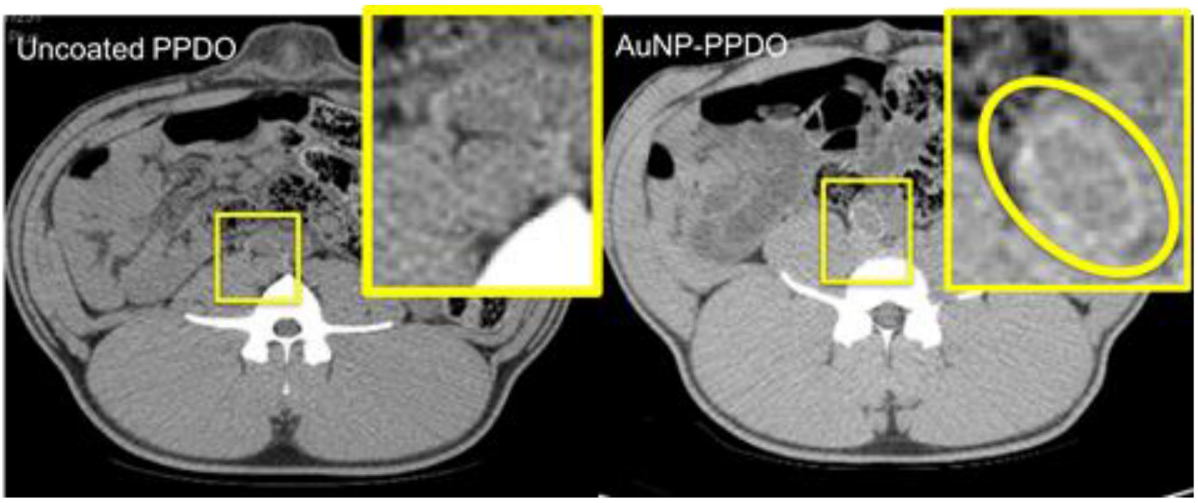


Figure 6.

CT image (axial view) of the pig deployed with the uncoated and AuNP-coated PPDO where the inset shows the filter location. The stent ring had increased radiopacity with AuNP-PPDO IVCF compared with the uncoated one.

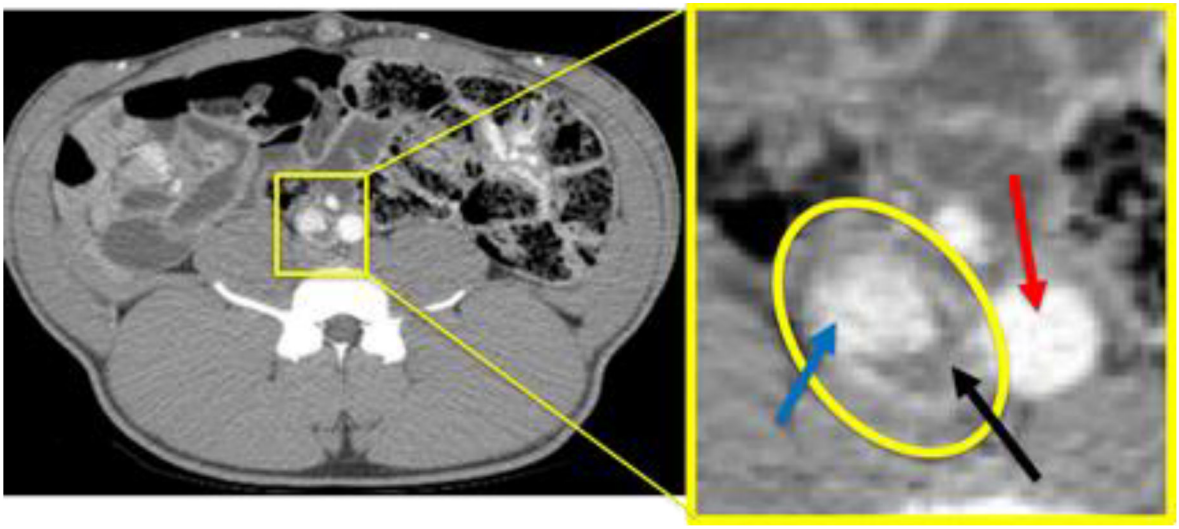


Figure 7.

Axial CT image of the pig deployed with the AuNP-PPDO IVCF after clot introduction in the presence of iodine based contrast agent. The inset shows the zoomed-in image of the IVCF location. The yellow circle defines the stent of the AuNP-PPDO IVCF. The iodine contrast shows blood flow in the IVC (blue arrow) and the aorta (red arrow). The black arrow shows the clot that was introduced and was confined within the AuNP-PPDO IVCF.

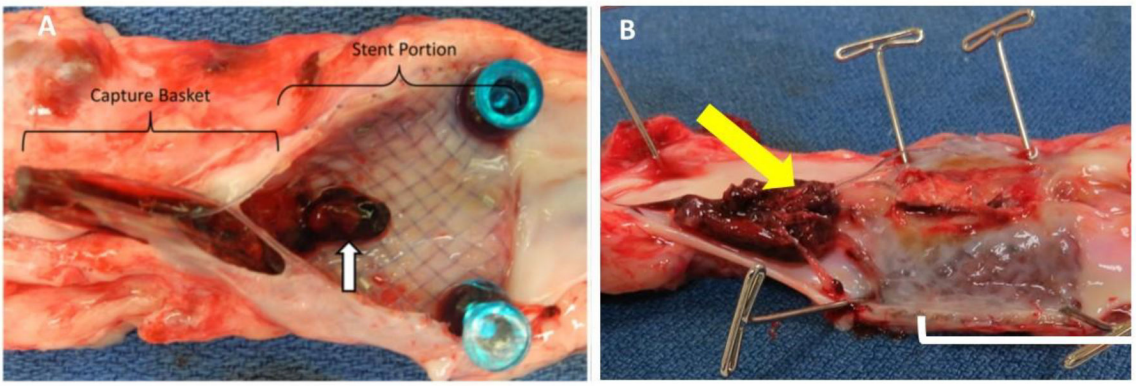


Figure 8.

Pig necroscopy after control and AuNP-IVC filter implantation. (A) PPDO IVCF [3]. The stent has been endothelialized into the vessel wall, and the remnant thrombus is still captured in the filter 19 days post deployment; (B) AuNP-IVC filter group, two weeks post implantation. The yellow arrow indicates the introduced blood clot was still captured in the AuNP-IVC filter basket. The white bracket outlines the stent portion of the AuNP-IVC filter. The IVC wall of the stent portion is remarkably darker than the control group, which could be from infused AuNPs. The black arrow indicates the broken strand of the filter, which abraded endothelial surface, with the resultant thrombus formation.

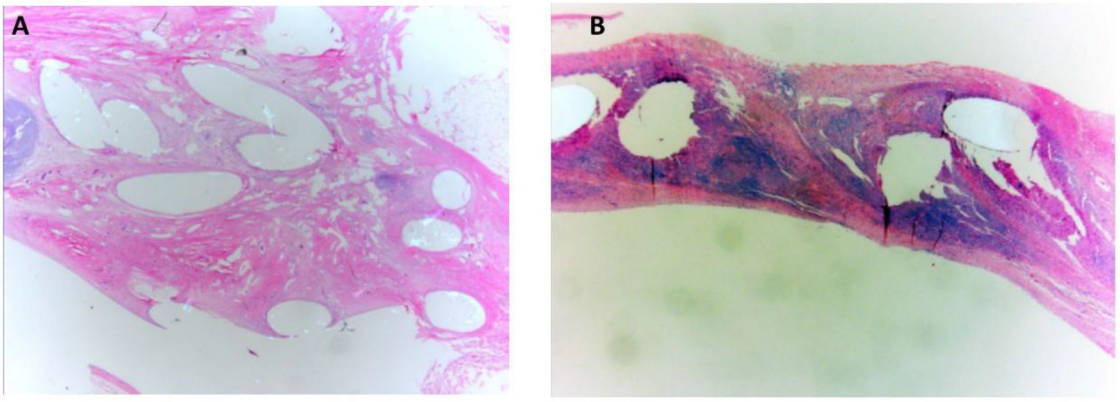


Figure 9.

Hematoxylin and eosin (H&E)-stained sections of IVC containing the absorbable filter. (A) Control IVC filter group, 10 weeks post implantation; (B) AuNP-IVC filter group, two weeks post implantation.